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10/591,195	09/29/2006	Liat Hayardeny	2609/68051-B-PCT-US/JPW/J	7371

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,195	HAYARDENY ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9,10,12-17,22,27-30,46-48 and 111* is/are pending in the application.

4a) Of the above claim(s) *46-48 and 111* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9,10,12-17,22 and 27-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/11/08,4/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks filed 2 June 2008 have been entered. No claims have been amended. Claims 1 – 5, 9 – 10, 12 – 17, 22, 27 – 30, 46 – 48, and 111 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group I (claims 1 – 5, 9 – 10, 12 – 17, 22, and 27 – 30) in the reply filed on 2 June 2008 is acknowledged. The traversal is on the ground(s) that

A) The examiner has failed to provide evidence that the claimed inventions are independent and distinct;

B) The reference cited by the Examiner (Polman WO 00/74676) "contains a laundry list of agents useful in treating multiple sclerosis which includes glatiramer acetate" and that co-administration of two drugs is potentially problematic; and

C) Examination of all claimed inventions is proper even if those inventions are independent and distinct, if search and consideration of all inventions can be made without serious burden.

This is not found persuasive for the following reasons:

With respect to A), the discussion of whether inventions are independent and distinct applies only to applications filed under 35 USC § 111, not to national stage applications of international applications filed under 35 USC § 371; see MPEP § 801. This application was filed under 35 USC § 371, thus the criterion cited by applicant (whether inventions as claimed are independent and distinct) is not germane. However, even if it were, the inventions would be considered to be related as product and process of using, and could be properly restricted as set forth in MPEP § 806.05(h).

With respect to B), the examiner disagrees with applicant's characterization of glatiramer acetate as one of a laundry list of agents. Glatiramer acetate is synonymous with copaxone, which is one of a small number of agents listed to be added to 2-amino-6-trifuromethoxybenzathiazole. Whether or not the combination has a predictable or unpredictable activity is not relevant, since the prior art reference by Polman teaches every element recited in instant claim 1.

With respect to C), examination of the two inventions together would require serious search burden. Reasons for determining that there would be a serious search burden if restriction were not required include, but are not limited to:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

At the very minimum, different non-prior art issues are likely to be raised by the invention of groups 1 and 2 as set forth previously. Consideration of Group 1 requires consideration of enablement of treatment of every single disease recited in claim 3, which is not required for consideration of claims drawn to products (i.e., Group 2). As consideration of the two inventions requires consideration of different issues, restriction is proper.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 46 – 48 and 111 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2 June 2008.

4. Claims 1 – 5, 9 – 10, 12 – 17, 22, and 27 – 30 are under examination.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Browser-executable code appears on pp. 59 – 63 for example. Applicant should ensure that all browser-executable code is deleted from the application. This can be accomplished by deleting the text "http://" from each web address.

Information Disclosure Statement

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892 or by applicant in one of the information disclosure statements of record, they have not been considered.

7. The IDSs filed 11 February 2008 and 7 April 2008 have been considered. The examiner is unable to determine if reference 54 on the IDS filed 11 February 2008 constitutes prior art, as no publication date is listed on either the IDS or the reference itself.

8. Reference 46 on the IDS filed 11 February 2008 has not been considered. No copy of the reference has been provided.

9. Reference 50 on the IDS filed 11 February 2008 has not been considered. It is unclear whether the reference is to a journal article by Bornstein, or to a US patent (5,800,808) as both are listed. Additionally, no copy of the reference by Bornstein has been provided. Note that the '808 patent has been considered as it is separately listed on the IDS.

Claim Objections

10. Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 3 depends from claim 2, which is limited to treating a neurodegenerative disease. However claim 3 recites many conditions which are not neurodegenerative diseases, including for example "a nutritional metabolic disorder, acute glaucoma" and "systemic lupus erythematosus"

11. Claim 1 objected to because of the following informalities: it has two periods, one in line 13, after the word "subject" and one at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 – 3, 13 – 17, 22, and 27 – 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of neurological diseases and conditions including amyotrophic lateral sclerosis and multiple sclerosis, does not reasonably provide enablement for treating neurodegerative diseases as broadly set forth in claim 3 or for providing protection against toxic levels of MAO-B activity as set forth in claim 13, or for treatment of disease by administering ineffective doses of the drugs as encompassed by claim 16. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

In this case, the nature of the invention is complex. The claims encompass treatment of any and all neurodegenerative disease (see claim 2 for example) and providing protection against toxic MAO-B activity (see claim 13). The claims are broad in that, with the exception of claims 4 – 5, they encompass either a large number of diseases (see claim 3) or an unlimited number of possible conditions (claim 1). The specification offers up a series of prophetic examples of treatment of various diseases (see for example pp. 37 – 57) but does not provide reduction to practice or working examples of treatment of diseases. Thus what is claimed is considerably broader than what is disclosed in terms of examples.

The art recognizes that compositions comprising glatiramer acetate are useful for treatment of several neurological diseases. See for example Eisenbach-Schwartz U.S. Patent 7,351,686 (issued 1 April 2008, based on an international application filed 5 December 2002), particularly claims 1, 6, and 10 - 11, which are drawn to treatment of ALS by administration of glatiramer acetate (also called copolymer 1) and 2-amino-6-trifuromethoxybenzathiazole (also called Riluzole). See also Eisenbach-Schwartz, U.S. Patent 6,844,314 (issued 18 January 2005, filed 22 January 2001), which teaches that compositions comprising copolymer 1 protects against glutamate toxicity (column 6 line 45), treats multiple sclerosis (paragraph spanning

columns 4 – 5), as well as traumatic brain injury, stroke, and glaucoma (column 6 lines 28 - 40). The references teach that the mechanism of action of copolymer-1 is to protect neurons from secondary damage by inducing a form of protective autoimmunity. Thus it is reasonable that the instant specification is enabling for treatment of specific diseases recited in claims 3 - 5 that are primarily characterized by damage to neurons.

However, the specification as filed is not enabling for treatment of nutritional metabolic disorders and lupus as recited in claim 3. These diseases share no common etiology or mechanism either with each other or with those diseases and conditions that have been shown to be treated by administration of compositions comprising either Riluzole or copolymer-1. Additionally, the specification provides no evidence of providing protection against toxic levels of monoamine oxidase-B activity, as recited in claim 13. The specification fails to provide guidance as to what levels of MAO-B are toxic, and does not indicate what additional steps or starting materials should be used in the method of claim 13 in order to provide protection. The specification does not provide guidance as to how to select patients with MAO-B toxicity. Thus the skilled artisan would have to determine how to identify such patients on his or her own, and then determine what should be undertaken in order to provide protection against MAO-B toxicity.

Additionally, the specification fails to provide guidance as to selection of doses of glatiramer acetate and riluzole which are not effective to provide neuroprotection, as recited in claim 16. The specification does not provide working examples of treatment of disease by administering ineffective doses of these drugs, and provides no evidence, either in vitro or in vivo, of any synergistic effect of the drugs. The skilled artisan would immediately understand that those doses which are ineffective for providing neuroprotection will not, by definition, provide protection. The specification fails to provide working examples of treating disease or providing neuroprotection by administering doses known to be ineffective. Thus the skilled artisan would have to resort to undue experimentation in order to overcome the art-recognized hurdle of eliciting an effect by administering an ineffective amount of a drug.

As the art recognizes that certain classes of disorders are amenable to treatment with these drugs, and the specification fails to show actual reduction to practice of treatment of diseases other than what was known in the art, given the complex nature of the invention and the lack of guidance set forth in the specification, the skilled artisan would be unable to treat all the diseases claimed in the absence of undue experimentation. Since there is no

demonstration of success, even in animal models, in this very complex and unpredictable field, the artisan would be unable to carry out the full scope of the invention without resorting to trial and error experimentation.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 – 3, 5, 12 – 14, and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Eisenbach-Schwartz (U.S. Patent 7,351,686, issued 1 April 2008, PCT filed 2 December 2002, claiming benefit of a provisional application filed 6 December 2001).

Eisenbach-Schwartz teaches treatment of ALS, encompassed by claims 1 - 3 and recited in claims 3 and 5, by coadministration of copolymer 1 (also known as glatiramer acetate; see ‘686 patent column 10 lines 39 – 49) and 2-amino-6-trifuromethoxybenzathiazole (also called Riluzole). See for example '686 patent column 5 lines 6 - 12 and lines 25 - 27 as well as claims 1, 6, and 10 - 11. As the reference teaches administration of the same drugs to the same patient populations recited in instant claims 1 - 3 and 5, those claims are anticipated. Claims 12 – 13 are included in this rejection as they do not recite additional steps to be taken or drugs to be administered, but rather recite effects which will occur upon administration of the drugs. Claim 14 is anticipated as Eisenbach-Schwartz specifically teaches treatment of humans (column 5 lines 6 - 21). Claim 15 is anticipated as Eisenbach-Schwartz teaches administration of 80 mg once a month (column 11 line 30 – 39), which is effective on its own for treatment of ALS, and also indicates that 100 mg of Riluzole should be administered (column 11 lines 44 - 49), which is presumed to be effective absent evidence to the contrary. Claim 17 is anticipated

as the dose taught by the reference (80 mg once a month) is within the range recited in claim 17.

14. Claims 1 – 4, 12 – 13, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Polman (WO 00/74676, published 14 December 2000, of record).

Polman teaches co-administraton of 2-amino-6-trifuromethoxybenzathiazole (also called Riluzole) and copoaxone (also called glatiramer acetate) for treatment of multiple sclerosis; see for example p. 2 lines 15 – 30. This anticipates every element of claims 1 – 4. Claims 12 – 13 are is included in this rejection as they do not recite additional steps to be taken or drugs to be administered, but rather recite effects which will occur upon administration of the drugs. Claim 15 is anticipated as it is presumed that both the amounts of the drugs administered are sufficient to treat disease, absent evidence to the contrary. Note that no particular doses are recited in claim 15. As the claim recites no more than what is taught in the prior art, the claim is anticipated.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 9 – 10, 12 – 15, 17, 22, and 27 – 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eisenbach-Schwartz (U.S. Patent 6,844,314, issued 18 January 2005,

filed 22 January 2001, claiming benefit of earlier-filed applications) in view of Sinciscalchi 1999 (Synapse 32:147-152).

Eisenbach-Schwartz teaches administration of glatirmaer acetate (also known as copolymer 1) for treatment of disease and protection of injury following stroke, which is on point to claims 1 and 9 - 10. See for example column 6 lines 27 - 35. However Eisenbach-Schwartz does not explicitly teach administration of riluzole, as encompassed by claim 1.

Sinciscalchi teaches that riluzole (also known as 2-amino-6-trifuromethoxybenzathiazole) protects against ischemia-induced cell death in an in vitro model of this condition. See Results section of the reference. Sinciscalchi also teaches that the data indicate that the drug should be used in patients for treatment of ischemia (i.e., stroke). However Sinciscalchi does not teach actual administration of the drug to patients, and does not teach administration of glatiramer acetate as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to co-administer copolymer-1 and riluzole, thereby arriving at the inventions of claims 1 and 9 – 10, with a reasonable expectation of success. It is prima facie obvious to co-administer two compounds known to be effective for the same purpose; here copolymer-1 is shown to be effective for protecting against stroke in vivo, and riluzole is shown to be effective in vitro. Claims 12 – 13 are is included in this rejection as they do not recite additional steps to be taken or drugs to be administered, but rather recite effects which will occur upon administration of the drugs. Claim 14 is included in this rejection as Eisenbach-Schwartz teaches administration to humans (see paragraph spanning columns 18 – 19), and it would have been obvious to treat humans with riluzole as well as explained above. Claim 15 is included in this rejection as it is presumed that both the amounts of the drugs administered are sufficient to treat disease, absent evidence to the contrary. Note that no particular doses are recited in claim 15, and that optimization of doses is generally considered obvious. Similarly, claims 17 and 22 are included in this rejection as optimization of the dose is obvious; see also column 22 lines 1 - 40. Claims 27 – 28 are included in this rejection as changing the order of treatment would not be expected to have an influence on the efficacy; see MPEP § 2144.04(IV).

16. Claims 1 – 3, 5, 12 – 14, 17, and 29 – 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eisenbach-Schwartz (U.S. Patent 7,351,686) in view of Bensimon 1994 (New England Journal of Medicine 330:585-591).

The reasons why claims 1 – 3, 5, 12 – 14, and 17 are anticipated by Eisenbach-Schwartz are set forth in the rejection under 35 USC 102(e) above. Briefly, the reference teaches treatment of ALS by coadministration of copolymer 1 (also known as glatiramer acetate; see '686 patent column 10 lines 39 – 49) and 2-amino-6-trifuromethoxybenzathiazole (also called Riluzole). See for example '686 patent column 5 lines 6 - 12 and lines 25 - 27 as well as claims 1, 6, and 10 - 11. Eisenbach-Schwartz specifically teaches subcutaneous administration of copolymer-1 is a preferred route of administration (see column 11 lines 40 – 43 and column 12 lines 10 - 16), which is on point to claims 29 and 30. While Eisenbach-Schwartz teaches that riluzole should be co-administered for treatment of ALS, the reference does not explicitly specify that the oral route should be selected, as recited in claims 29 - 30.

Bensimon teaches that 100 mg riluzole per day, delivered by the oral route, increases survival at one year in patients with ALS and indicates that the drug slows disease progression. See abstract (spanning pp. 1 – 2 of the printed version of the article, enclosed) for statement of efficacy, and p. 3 second complete paragraph for teaching that the dose was delivered orally. This is on point to claims 29 - 30. However Bensimon does not teach administration of glatiramer acetate as recited in claims 1 and 29.

It would have been obvious to one of ordinary skill in the art to select the oral route of administration of riluzole, as taught by Bensimon, when performing the method of Eisenbach-Schwartz, who teaches co-administration of that drug with glatiramer acetate delivered subcutaneously for treatment of ALS. The motivation to do so would be to use a route known to be effective, thereby obviating the need for experimentation and instead being able to treat patients effectively.

Conclusion

17. No claim is allowed.

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Polman U.S. Patent 6,872,739. This patent issued from the national-stage entry of the international application that formed the basis of the Polman WO 00/74676 reference. Note the '739 patent claims the same patentable invention as set forth in certain pending claims.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker, Ph.D./
Patent Examiner, Art Unit 1649
August 19, 2008